Validation

Neurogastroenterol Motil (2013) **25**, e315–e323 doi: 10.1111/nmo.12109

An oropharyngeal pH monitoring device to evaluate patients with chronic laryngitis

E. S. YUKSEL,* J. C. SLAUGHTER,† N. MUKHTAR,* M. OCHIENG,* G. SUN,* M. GOUTTE,* S. MUDDANA,* C. GAELYN GARRETT‡ & M. F. VAEZI*

*Division of Gastroenterology, Hepatology and Nutrition, Nashville, TN, USA
†Department of Biostatistics, Nashville, TN, USA
‡The Vanderbilt Voice Center, Nashville, TN, USA

Abstract

Background *Diagnostics for gastro-esophageal reflux disease (GERD) are suboptimal because of limited sensitivity. We performed in vitro and in vivo studies to systematically assess the performance characteristics of an oropharyngeal pH probe.* ***Methods*** *In vitro studies compared the oropharyngeal probe with a standard pH catheter in liquid and aerosolized solutions, pH 1–7. The accuracy of measurements, deviation from target pH, and time to equilibrium pH were determined. Simultaneous distal esophageal pH measurements were obtained in 11 patients with GERD. Oropharyngeal and distal esophageal reflux parameters were measured for controls (n = 20), patients with GERD (n = 17), and patients with chronic laryngitis (n = 10).* ***Key Results*** *In the liquid phase, at pH 4–5, the oropharyngeal probe had less deviation from the target value than the standard catheter; deviation in the vapor phase was similar (0.4 pH units). Median (interquartile) time to reach equilibrium pH was significantly (P < 0.001) faster with the oropharyngeal than the standard probe. In comparing simultaneous distal esophageal pH characteristics, 96% of recordings with the new and standard probes were in agreement to within ±1.0 pH unit; 71% of recordings were in agreement within ±0.5 pH units. Patients with chronic laryngitis had significantly higher levels of oropharyngeal acid exposure at pH <4, <5, and <6, in the upright position than patients with GERD or controls (P < .001).* ***Conclusions & Inferences*** *Oropharyngeal pH monitoring appears to be more sensitive than traditional pH monitoring in evaluation of patients with extraesophageal reflux. It is a promising tool in evaluation of this difficult group of patients.*

Keywords *diagnosis, esophageal acid exposure, heartburn, Restech.*

Address for Correspondence
Michael F. Vaezi, Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, 1660 TVC, 1301 -22nd Ave. South, Nashville, TN 37232-5280, USA.
Tel: 615 322 3739; fax: 615 322 8525;
e-mail: michael.vaezi@vanderbilt.edu
Received: 6 December 2012
Accepted for publication: 8 February 2013

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a common chronic disorder with increasing prevalence affecting up to 40% of adults in the US population.[1] It typically manifests as heartburn and/or regurgitation and remains the leading outpatient physician diagnosis for gastrointestinal disorders in the United States.[2] Extraesophageal symptoms such as chronic cough, asthma, laryngitis, and globus may also be alternate manifestations of GERD.[3–5] Esophageal acid exposure in this group may or may not be accompanied by the presence of typical reflux symptoms such as heartburn and regurgitation.[6,7] Vagaries of its presentation and lack of an objective diagnostic gold standard in patients with extraesophageal symptoms often begets extensive evaluation involving multiple specialty consultations, procedures, diagnostic tests, and medication use with projected annual healthcare utilization of over $50 billion.[8] In addition, pH monitoring in the distal and proximal esophageal or hypopharyngeal regions are limited with low diagnostic sensitivities.[9,10] Thus, there is an unmet need to identify a more sensitive and specific diagnostic test in which patients' symptoms may be more directly linked to physiologic reflux.

Recently, a minimally invasive pH probe was developed to measure reflux in the oropharynx of patients with suspected extraesophageal symptoms presumed to be GERD related.[11,12] The device utilizes a 1.5-mm diameter catheter, a specially designed

sensor, and a unique flashing LED light to guide the catheter into proper position in the posterior oropharynx above the upper esophageal sphincter (UES). This innovative feature negates the need for manometry or endoscopy and its sensor design allows for capturing liquid reflux events as well as purported aerosolized acid exposure.[11,13,14] Employing this device, Wiener *et al.*[11] studied 15 patients with laryngopharyngeal reflux (LPR) reporting an increasing pH gradient from the distal esophagus to the oropharynx with the latter often occurring at pH values above 4, suggesting that the traditional pH catheters and criteria may be misleading in identifying true reflux-related events in this group of patients. In addition, in a study of 10 patients with LPR, Kawamura *et al.*[15] suggested that the majority of pharyngeal reflux events were gaseous in nature, signifying insensitivity of the currently employed pH probes in detecting aerosolized reflux events in patients with extraesophageal symptoms. To date there are no validation studies evaluating the relative accuracy of oropharyngeal pH monitoring to substantiate its clinical benefit.

Thus, we performed a series of bench-to-bedside three-stage systematic studies to determine the clinical utility of this new probe. Stage 1: *In vitro* performance characteristics of the new oropharyngeal pH device were compared with the current standard probe at pH ranges of 1–7 in both liquid and vapor phases employing a novel esophageal vapor simulator. Stage 2: We compared simultaneous probe performance relative to the standard pH probe in the distal esophagus of patients with GERD; and Stage 3: prevalence of oropharyngeal and distal esophageal reflux was measured with the new probe in three different study groups; healthy volunteers, patients with classic GERD symptoms, and those with LPR.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board at Vanderbilt University. Informed consent was obtained from all study participants (IRB #060860; NCT 00388453). The senior author (MFV) and co-authors had access to the study data and had reviewed and approved the final manuscript.

Stage 1

In vitro *liquid phase experiments* Simultaneous pH measurements, using the oropharyngeal pH probe (Restech, Dx-pH San Diego, CA, USA) and a conventional pH catheter (Sandhill Scientific Inc., Denver, CO, USA), both antimony in type, were obtained following time synchronized immersion in buffer solution of pH 1–7 for 5-min intervals. Nine trials were conducted in each buffer solution. Each trial was conducted in a water bath maintained at 37 °C, with the average buffer solution at 37 °C at the beginning of each trial. Each of the pH probes were immersed in a pH 7 buffer solution between measurement periods. The accuracy of pH measurement (deviation form target pH) and time elapse to achieve equilibrium pH were determined for each probe. The equilibrium pH was defined as the median pH value of all measurements obtained between 30 and 150 s following immersion in each pH buffer solution. All experiments were performed after appropriate calibration of both probes and time synchronization of the internal clocks of both recorders.

In vitro *vapor phase experiments* Simultaneous pH measurements were obtained with the oropharyngeal and conventional pH catheter employing a novel esophageal vapor simulator (Fig. 1). This system consisted of a straight tube that projected from a sealed buffer reservoir that was connected to three systems independently controlling humidity, temperature, and airflow through the simulated esophagus. An ultrasonic vaporizing unit within the reservoir was used to deliver aerosolized buffer solutions up the simulated esophagus at a flow rate of approximately 1.5–2 L min^{-1} to resemble esophageal flow due to GERD. Humidity was maintained at 100% and the average temperature within the tube was 37 °C, as measured at the start of each trial. The oropharyngeal and Sandhill probes were clipped together so that the measuring electrodes were at the same location and inserted at a depth of 30 cm from the opening and were exposed to aerosolized buffer solutions of pH 1 through pH 7 for 5-min intervals. Nine trials were completed in each aerosolized buffer solution. The pH probes were maintained in a pH 7 buffer solution between periods of measurement. The accuracy of pH measurement (deviation from target pH) and time taken to achieve equilibrium pH were determined for each probe. The equilibrium pH was defined as the median pH value of all readings obtained

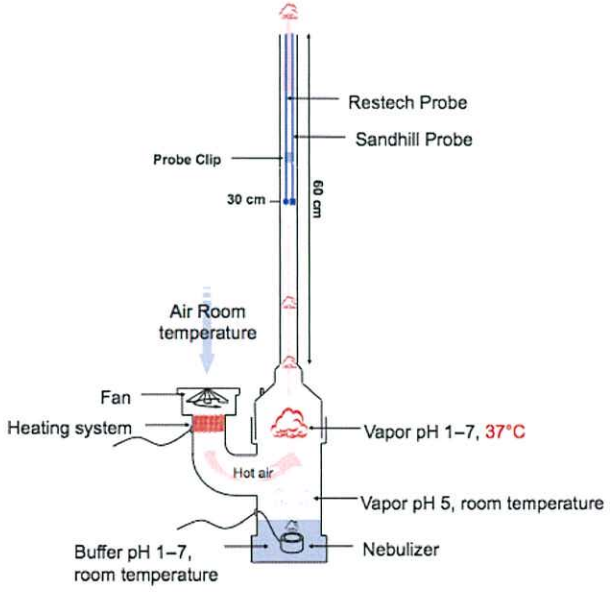

Figure 1 Illustration of the vapor phase esophageal simulator. The device consisted of a straight tube projecting from a sealed buffer reservoir connected to three systems independently controlling humidity, temperature, and airflow through the simulator esophagus. The conventional (Sandhill) and oropharyngeal (Restech) pH probes were positioned 30 cm inside the 60 cm simulated esophagus and they were exposed to vaporized solutions ranging in pH from 1 to 7.

between 30 and 150 s following exposure to each aerosolized buffer solution.

Stage 2

The relative performance of the oropharyngeal pH probe to that of the conventional pH probe was studied in 11 patients with GERD who underwent simultaneous distal esophageal pH monitoring. All GERD patients had chief complaints of heartburn and regurgitation and a prior history of esophagitis by the LA Classification who were symptomatically controlled on once daily proton pump inhibitor (PPI) therapy. Patients discontinued any acid-suppressive therapy 7–10 days prior to undergoing pH testing. As the oropharyngeal pH catheter is typically only 46 cm in length, a special 91-cm-long oropharyngeal pH probe catheter was manufactured to allow positioning in the distal esophagus. The oropharyngeal and the conventional pH probes were positioned concurrently 5 cm above the manometrically measured lower esophageal sphincter (LES) based on a previously reported protocol.[12] Ambulatory pH measurements were then obtained for 18–24 h off acid-suppressive therapy. Probe performance, agreement, and divergence were then compared between the two pH catheters.

Stage 3

Performance of the new oropharyngeal probe was tested in three different study populations; (i) healthy volunteers; (ii) patients with GERD; and (iii) patients with LPR. The three groups were recruited from the Vanderbilt Medical Center between June 2008 and June 2011. Healthy volunteers included individuals without current or prior diagnosis of GERD or extraesophageal symptoms and had never been on any acid-suppressive therapy including histamine receptor antagonists (H2RA's) or PPIs, or used antacids (Rolaids, Tums, Pepto-Bismol, etc.). Patients were defined to have GERD if they had a history of GERD symptoms (heartburn and/or regurgitation) at least once in a week in the past month and had an improvement of their symptoms with PPI use and if they had erosive esophagitis by LA classification at endoscopy. Patients with LPR included those suspected to have reflux-related laryngeal symptoms, including chronic cough, throat clearing, and hoarseness. This group of patients included current non-smokers with unremarkable chest radiographs who had undergone extensive testing and exclusion of other common causes for their laryngeal symptoms by the Vanderbilt Allergy, Sinus and Asthma Program (ASAP), and Vanderbilt Voice Center (spirometry, methacholine challenge, sputum eosinophil count, otolaryngology examination, high-resolution computerized tomography scan of the thorax and sinuses, and allergy testing). All patients were excluded if under 18 years of age, pregnant, had undergone surgery for reflux or peptic ulcer disease, had an esophageal motility disorder, or if they had a serious illness that would interfere with study participation. All acid-suppressive therapies were discontinued for 7–10 days prior to any testing.

The three study groups underwent dual pH measurements of the oropharyngeal as well as esophageal acid exposure employing the regular length probe for the oropharynx (Restech) and the custom-designed long Restech probe for the distal esophagus. The reason for the custom-designed esophageal measurement was to ensure that events noted in the oropharynx originated distally and were of gastric source. Measurements for the two locations were time synchronized to ensure accuracy. The standard short catheter was visually placed in the oropharynx at the level of the uvula per instruction by the manufacturer and the esophageal probe tip was placed 5 cm above the manometric LES. Each subject was asked to wear the device for a 24-h period and was encouraged to participate in normal daily activities. Subjects carried two transmitter receivers, one for each of the catheters (esophageal and oropharyngeal). Each catheter contained a transmitter, which wirelessly sent the data to a separate monitor worn by the patient, recording events marked for meals, position, and chief complaint. Once the pH study was completed, the catheters were removed, the data from the digital recorder were downloaded to a password-protected computer, and the data were analyzed with DataView software provided by the manufacture. The software generated a graphical tracing of the study events for both the oropharyngeal and esophageal locations and also created a report of any reflux events.

Statistical analysis

Data were collected and stored at the secure site with strict control and supervision of data entry and access to the study. The in vitro data in stage 1 were analyzed employing the Wilcoxon signed rank test to compare differences in the paired data. Linear regression models were used to determine the mean difference in equilibrium pH achieved by the devices in each buffer solution. For stage 2, individual patient data were analyzed employing Bland–Altman plot to determine agreement between the new oropharyngeal and the conventional Sandhill probe. Using plots of the difference in pH measurements *vs* the average value obtained by the two devices (the best estimate of the true, unknown pH value at any given time), the level of agreement as a function of both true pH and time of day were determined.

For stage 3, the percent time spent below a pH of 4, 5, and 6 was determined for each probe. These calculations were separated based on the length of time spent in the upright position, supine position, and a combination of the two positions (total). The distribution of percent time was summarized using the median (IQR) for each concentration of pH and body position. All data were visually evaluated for accuracy by the senior investigator (MFV) who was blinded to study groups, and subjects were excluded if they were not monitored for at least 12 h. The data were compared among the three study groups for esophageal and oropharyngeal parameters. Reflux event was calculated for a drop in pH from baseline to either <4, or <5, or <6 and each event had to last more than 5 s and could not be during the meals. A true oropharyngeal event was considered to occur only during a period of synchronous distal esophageal acid event, abrupt pH decrease (onset of pH decrease to nadir pH <30 s). Oropharyngeal events occurring outside the criteria described above were considered 'artifacts' and their rates were calculated and expressed as percentage of total reflux events. The criteria for reflux events described were similar to those previously reported for hypopharyngeal pH monitoring.[16] The same threshold was used for distal and oropharyngeal probes to define reflux events. Wilcoxon tests were used to compare pH values. A Bonferroni correction for the two statistical tests was used so that P value <0.025 was considered significant.

Role of funding source

The protocol was an independent Investigator Initiated Study funded by Respiratory Technology Corporation (Restech) but conceived by the PI (MFV). Restech provided funding for the study

coordinator, and patient compensation. The funding source had no role in the study design, conduct, data collection, statistical analysis, manuscript preparation or review, interpretation or decision to submit the manuscript for publication.

RESULTS

Stage 1

In vitro *liquid and vapor phase experiments* There was a significant (P < 0.001) difference in deviation from equilibrium pH between the two pH probes in the liquid phase (Table 1 and Fig. 2A). The conventional probe overestimated the true pH value by a median (IQR) of 0.50 (0.30–0.60) pH units, whereas the oropharyngeal probe underestimated the true pH [0.00 (−0.38 to 0.45)]. The oropharyngeal probe had less deviation from the solution pH at pH 4 and pH 5 (Fig. 2A). Deviation from target pH in the *vapor phase* was similar (P = 0.3) for the two probes (0.4 pH units) (Table 1) (Fig. 2B); however, Median (IQR) time to reach equilibrium pH (seconds) was significantly (P < 0.001) faster with the oropharyngeal than with the conventional probe both in the liquid and vapor phases [Liquid phase: 5.5 (2.5–11) *vs* 21.0 (3.5–46); Vapor phase: 16 (3.0–34) *vs* 57 (30–75); respectively] (Table 1) (Fig. 2C and D). Deviation from and time to equilibrium pH were significantly (P < 0.001) less in the liquid than in the vapor phases for both the conventional and the oropharyngeal probes.

Stage 2

Eleven patients with GERD (45% male, mean age 41 years, range 21–59 years) underwent ambulatory pH monitoring with concurrent conventional and custom-designed long length oropharyngeal pH probes positioned in the distal esophagus. Figure 3 represents single subject data with superimposed graph for the two probes. There was a strong correlation ($r = 0.91$) between pH values detected by the two probes (Fig. 4A); 96% of recordings agreed to within ±1 pH unit and 71% within ±0.5 pH units. There was no statistically significant difference between the two probes for detection of number of reflux events at pH <4, <5 or <6 cutoff values; however, the oropharyngeal pH probe spent consistently more time at pH < 4 (P = 0.2), pH < 5 (P = 0.05), and pH < 6 (P = 0.01). The greatest divergence between the two probes occurred when: (i) the pH value was around 4 (oropharyngeal pH detecting more events) (Fig. 4A); or (ii) between the hours of 12 a.m. and 6 a.m. in the supine position (Fig. 4B).

Table 1 Median (IQR) time to and deviation from equilibrium pH in liquid and vapor phases for the oropharyngeal (Restech) and conventional (Sandhill) pH probes

Parameters	Oropharyngeal probe	Conventional probe	*P*
Liquid phase			
Time to equilibrium pH (seconds)	5.5 (2.5–11)	21.0 (3.5–46)	<0.001
Deviation from equilibrium pH (pH units)	0.0 (−0.4 to 0.5)	0.5 (0.3–0.6)	<0.001
Vapor phase			
Time to equilibrium pH (seconds)	16 (3–34)	57 (30–75)	<0.001
Deviation from equilibrium pH (pH units)	0.4 (0.2–0.5)	0.4 (0.2–0.5)	0.3

Stage 3

The study population consisted of three groups: healthy volunteers [$n = 20$; median (IQR) age = 31 (26–40), 60% female]; GERD [$n = 17$, median (IQR) age = 38 (27–55), 65% female]; and patients with LPR [$n = 10$, median (IQR) age = 50 (39–66), 62% female]. Per definition, patients with GERD had significantly higher prevalence of heartburn (P = 0.01) and regurgitation (P = 0.004) and those with LPR who had significantly higher prevalence of cough (P = 0.01), throat clearing (0.001), and hoarseness (P = 0.001) with 45% having concomitant typical GERD symptoms but not as primary complaint.

Table 2 outlines the esophageal and oropharyngeal acid reflux parameters at three different pH cutoffs of <4, <5, and <6 for the three groups. Distal esophageal acid exposure was higher for patients with GERD and LPR as compared with controls at any of the pH cutoffs; however, it reached statistical significance (P = 0.02) only for patients with GERD in the supine position compared with healthy volunteers and LPR patients. Oropharyngeal acid exposure measured by% time pH less than 4, 5, or 6 was similar among the three groups (Table 2); however, LPR patients had significantly (P = 0.001) higher numbers of reflux events, predominately in the upright positions as compared with the other groups. Compared with normative data published for% total time pH <4, <5, and <6 cutoff values[12]; in the GERD group, 24%, 6%, and 0% of patients had abnormal reflux parameters, respectively, whereas in the LPR group, 25%, 12%, and 12% of patients, respectively, were abnormal. Similarly, for total number of reflux events for pH <4, <5, and <6 cutoffs, in the GERD group 12%, 18%, and 35% of patients, respectively, were considered abnormal and in the LPR group, 50%, 50%, and 37% of patients,

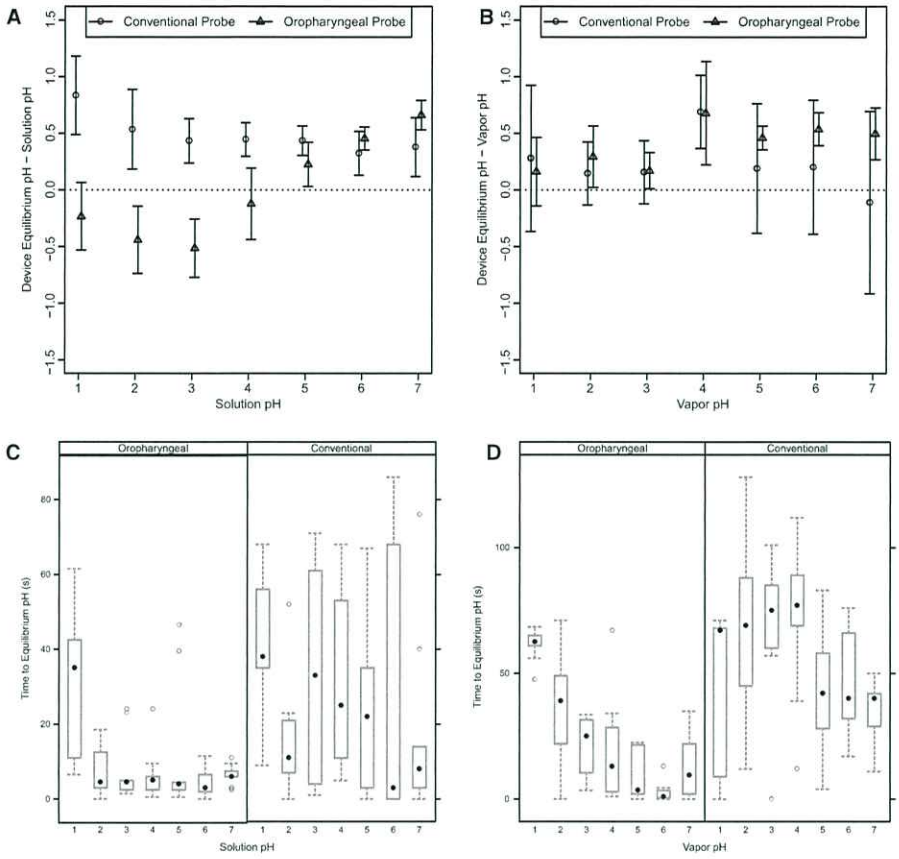

Figure 2 Deviation and time equilibrium in the liquid and vapor phases comparing oropharyngeal to conventional pH probe. In the *liquid phase*, the oropharyngeal probe had less deviation from the solution pH at pH 4 and pH 5 (A). Deviation from target pH in the *vapor phase* was similar for the two probes (B). Time to reach equilibrium pH (seconds) was significantly ($P < 0.001$) faster with the oropharyngeal than the conventional probe both in the liquid and vapor phases (C and D).

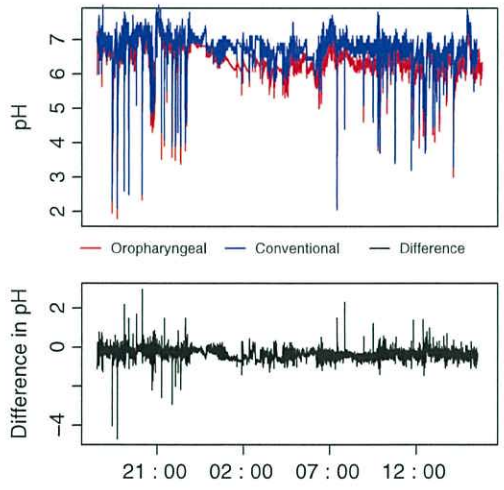

Figure 3 Superimposed esophageal pH tracing for the new compared with conventional pH probes (upper graph) and their subtracted differences (lower graph) in a patients with GERD in stage 2 protocol.

respectively, were abnormal. Only 3% of all reflux events detected by the oropharyngeal pH probe were considered 'artifact' (not preceded by a distal esophageal acid exposure) when pH <4 or <5 was employed as the cutoffs; however, this rate increased to 43% when pH <6 was used for the abnormal cutoff. Artifact was defined as any detected pH drop in the oropharynx, which was not accompanied by a temporally associated and equivalent drop in pH in the distal esophagus.

DISCUSSION

This is the first study to systematically investigate the relative accuracy and clinical utility of a new oropharyngeal pH monitoring device. In our bench-to-bedside in-depth protocols, we compared the new device to the traditional pH probe to: (i) determine its responsiveness and accuracy in detecting various pH values in both liquid and vapor phases, (ii) measure

esophageal reflux events concurrently with the traditional pH probe in patients with GERD, and (iii) determine both esophageal and oropharyngeal pH prevalence in healthy volunteers, patients with GERD and those with LPR. Our bench data show that in both liquid and vapor phases, the new oropharyngeal probe achieves the target pH significantly faster than the traditional probe. Although its deviation from the target pH values between 4 and 5 is less than the traditional probe in liquid phase, we did not find a difference between the probes in achieving the target pH values in the vapor phase. This finding is in contrast with suggested superiority of the oropharyngeal probe in the vapor phase relative to standard pH probes. Simultaneous esophageal measurement of reflux in patients with GERD showed that the two probes have excellent agreement in reflux detection; however, the new probe identifies more reflux below threshold pHs of 4, 5, and 6. Most interesting is the finding that the number of oropharyngeal reflux events in the upright position in patients with LPR was significantly more than those with GERD or healthy volunteers, while the distal pH parameters were similar between GERD and LPR patients. Thus, our study suggests that the new probe may offer added benefit in patients with LPR and possibly other extraesophageal symptoms.

In addition to the extensive in vitro validation studies, one unique aspect of our study is the use of a custom-designed long (Restech) catheter simultaneously positioned in the distal esophagus of three subject groups (healthy volunteers, GERD, and LPR) for internal consistency and to ensure that the decrease in pH detected by the oropharyngeal pH catheter originated distally and was of gastric source. Employing another pH probe catheter for the distal esophageal pH measurement would have introduced inevitable measurement error. The Restech sensor records pH values twice every second (2 Hz) whereas other pH devices detect esophageal pH values once every 4–6 s. This creates a potential for reflux events to be detected by the oropharyngeal probe and not by the distal esophageal catheter and erroneously be considered 'artifacts'. Using the same catheter in the distal esophagus as in the oropharynx in our study eliminated this clinically important source of inaccuracy. Our study design thus allowed for accurate measurement of the rate of 'artifact' reflux events detected by the oropharyngeal pH probe to determine if a distal esophageal probe is needed for future clinical trials. We found that only 3% of the reflux events would have been categorized erroneously by the oropharyngeal pH catheter as reflux, not detected first in the distal

Table 2 Esophageal and oropharyngeal pH parameters employing the new probe design comparing healthy volunteers, GERD and LPR patients

	pH < 4				pH < 5				pH < 6			
	Healthy volunteers	GERD	LPR	*P*	Healthy Volunteers	GERD	LPR	*P*	Healthy Volunteers	GERD	LPR	*P*
Distal esophageal % time												
Total	1.1 (0.5–3.9)	3.2 (1.5–8.7)	3.8 (1.8–6.7)	0.05	3.0 (1.9–8.3)	6.5 (4.4–27)	13 (3.6–19)	0.03	11 (8.6–27)	29 (12–54)	31 (19–58)	0.05
Upright	1.5 (0.8–4.2)	3.0 (1.8–9.1)	6.1 (2.7–12)	0.05	4.0 (2.9–9.7)	7.9 (4.1–14)	20 (5.5–27)	0.05	11 (7–22)	26 (11–41)	35 (10–60)	0.06
Supine	0.1 (0.0–0.9)	1.1 (0.1–6.9)	0.2 (0.0–1.7)	0.05	0.6 (0.0–2.8)	7.1 (0.7–30)	1.3 (0.0–6.1)	0.02	11 (4.6–27)	46 (15–75)	20 (4.6–52)	0.07
Oropharyngeal % time												
Total	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.3	0.0 (0.0–0.1)	0.0 (0.0–0.3)	0.2 (0.0–1.9)	0.1	5.6 (0.0–15)	6.8 (1.0–10)	10 (2–19)	0.7
Upright	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.2)	0.3	0.0 (0.0–0.0)	0.1 (0.0–0.2)	0.4 (0.0–2.3)	0.02	0.1 (0.0–1.4)	0.4 (0.01–0.8)	5.1 (0.0–19)	0.2
Supine	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.5	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.7	7.3 (0.0–22)	9.3 (2.7–20)	6.8 (0.1–19)	0.8
No. of events:												
Total	0.0 (0.0–0.0)	0.0 (0.0–0.0)	2.0 (0.0–5.5)	**0.003**	0.0 (0.0–0.2)	1.0 (0.0–1.0)	13 (2.5–29)	**0.001**	6.5 (0.0–35)	102 (5.0–181)	75 (45–177)	**0.005**
Upright	0.0 (0.0–0.0)	0.0 (0.0–0.0)	2.0 (0.0–2.2)	**0.001**	0.0 (0.0–0.0)	0.0 (0.0–1.0)	5.5 (2.5–26)	**0.001**	0.5 (0.0–10)	5.0 (2.0–12)	54 (28–95)	**0.001**
Supine	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.8)	0.07	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.8)	0.08	3.0 (0.0–12)	69 (1.0–161)	24 (3.5–63)	0.07

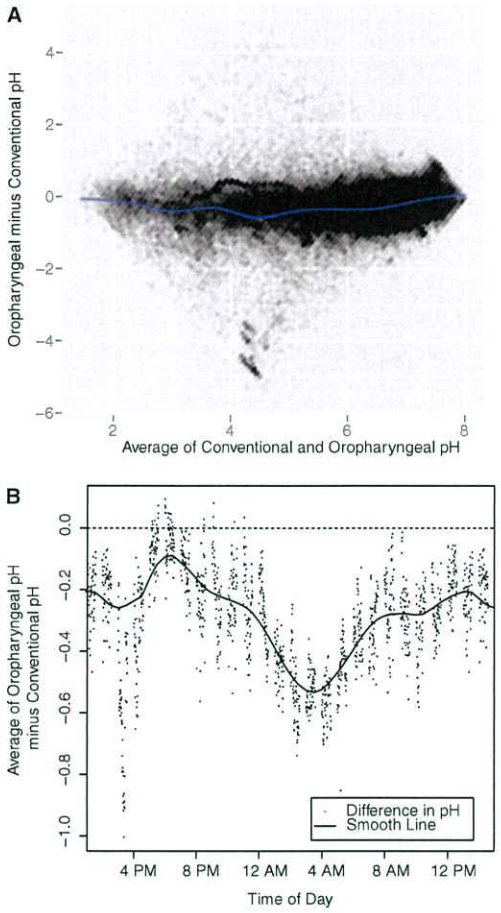

Figure 4 (A) Bland–Altman plot comparing individual patient pH data between the oropharyngeal and the conventional probes for stage 2 protocol. Disagreements between the pH readings for the two probes were greatest at pH values between 3 and 6. (B) Comparison of the two probes by time of day showing the greatest divergence occurring between the hours of 12 a.m. and 6 a.m.

esophagus. Thus, while it would be reasonable to employ only the oropharyngeal catheter given the low false-positive rate, we would still recommend close examination of the pH tracing for any events that may be meal related. While we employed distal esophageal probe, the benefit of using concomitant proximal esophageal and oropharyngeal pH probe is currently unknown and may need to be addressed in future studies. Avoiding an additional catheter traversing the UES may help eliminate discomfort associated with these probes and may reduce the 30% false-negative rate commonly associated with the traditional pH catheter measurements.[9,17,18]

The rapidity of pH sampling (twice every second) by the new oropharyngeal pH probe may be the reason for the in vitro study findings of faster reaching of the targeted pH in both the liquid and vapor phases (Fig. 4C and D). Moreover, this may explain the detection of higher oropharyngeal reflux events in LPR patients where in the past, hypopharyngeal pH catheters (sampling every 4–6 s) failed. One distinctive feature of the new probe is the fact that the reference and sampling electrodes are in close proximity while in the traditional pH probes they are separated, resulting in possible missed events especially if positioned in the hypo- or oropharynx. In addition, the traditional hypopharyngeal pH catheters are prone to drying out effects and may cause misleading results due to 'pseudo-reflux'.[19] The new oropharyngeal probe has a hydration monitor that automatically prevents inclusion of data due to 'pseudoreflux'. Despite the above unique characteristics of the new probe, we could not confirm that it has superiority in detecting vaporized liquid of various pH values (Fig. 4B), thus our studies suggest that an important benefit of the new pH catheter may be its sampling rate leading to possibly a more sensitive means of measuring reflux events in patients with extraesophageal reflux. The proof of its clinical utility will lie on its ability to predict response to acid-suppressive therapy based on the currently ongoing outcome studies.

The minimum pharyngeal or oropharyngeal acid exposure that is clinically relevant in patients with extraesophageal symptoms is currently unknown. Animal studies suggest sensitivity of the laryngeal tissue to various gastroduodenal contents including acid, pepsin, and bile acids.[20] However, the accuracy and reproducibility of traditional pH probes in the hypopharynx is less than optimal.[9,18] Hypopharyngeal and proximal esophageal pH monitoring have sensitivities of 40% and 55%, respectively.[17,18] This may be partly due to variability regarding position of proximal and hypopharyngeal pH probes (eg, 15 cm above the LES, within the UES, or above the UES), or visual *vs* manometric guided placement, or inadequate sampling rate. This difference results in heterogeneous findings and uncertainty regarding their clinical utility. More sensitive diagnostic means of identifying reflux events in the larynx would, indeed, be a welcomed change to our current diagnostic ability, especially if future studies show its reproducibility. The role of non-acid reflux in patients with extraesophageal reflux is uncertain. Recent study in a group of patients undergoing surgical fundoplication suggested that impedance pH testing did not predict response to fundoplication.[21]

The appropriate pH cutoff for normality employed in studies for GERD has traditionally been pH <4. This value was chosen for a number of reasons. It was found that the digestive enzyme, pepsinogen, is converted to its active form, pepsin, at or below a pH of 4.[22] Symptoms of heartburn often occur at or below this

pH. Studies of normal patients undergoing 24-h pH monitoring have shown that the pH of the esophagus is greater than or equal to 4 about 98.5% of the time[2,3]; however, the pH cutoff of 4 is contended, especially in patients with refractory GERD and those with extra-esophageal symptoms. In the latter group, earlier studies of LPR patients by Weiner *et al.* showed that there is a gradient of pH from distal esophagus to the oropharynx. In this study, 67% of reflux events in the distal esophagus were of acidic nature while the corresponding events in the oropharynx were less acidic by the traditional pH cutoff values of 4. The median pH in the oropharynx corresponding to pH< 4 in the distal esophagus was pH of 5.6. Thus, in this study, we provide data for pH <4, pH <5 as well as pH <6 cutoff values. Another reason to consider cutoff different from the traditional value of pH 4 is our data showing occasional delayed time to equilibrium with both the traditional as well as the oropharyngeal probes which may delay detection of actual refluxate pH with salivary neutralization to a higher pH value. We do not recommend the use of pH <6 cutoff values as we believe that this pH cutoff value may increase sensitivity of detecting more reflux events but it would significantly affect specificity of the diagnosis. As well based on our data, it is prone to including as high as 43% artifacts instead of true reflux events. However, future outcome data are needed to identify the best pH cutoff for this group. Consistent with prior reports in patients with LPR,[9] our data suggest that this group of patients reflux predominately in the upright position, suggesting disturbance in the transient LES relaxation mechanism.

Important limitations of our study include lack of prior validation studies on appropriate positioning of the oropharyngeal pH probe. The probe is usually placed visually and positioned approximately 5 cm above UES, but no manometry is required. Such positioning is prone to slight variation in placement resulting in increased variability. We recommend future studies to focus on this important clinical aspect of this probe. In addition, it was beyond the scope of this study to assess for the role of non-acid reflux in our study groups. Thus, we can provide any insight on the role of non-acid reflux in patients with LPR. Furthermore, it is important to recognize that the findings of abnormal reflux events in the oropharynx in patients with LPR do not suggest causality. Future outcome studies are needed to determine if abnormal oropharyngeal pH findings in this group predicts response to GERD therapy.

In conclusion, our in-depth study assessed the in vitro and in vivo responsiveness of the new oropharyngeal pH probe, showing increased sensitivity of the device at pH range of 3–5 with faster pH responsiveness and identification of more reflux events in the oropharynx of patients with LPR. The encouraging findings in our study must be followed by outcome data to evaluate if the use of this diagnostic test can predict response to acid-suppressive therapy in patients with extraesophageal symptoms.

ACKNOWLEGMENT

Dr. Vaezi had research grant support from Respiratory Technology Corporation for the conduct of this study.

FUNDING

A partial funding was provided by ResTech Inc., for the investigator initiated protocol.

DISCLOSURES

No conflict of interest for other authors.

AUTHOR CONTRIBUTIONS

ESY performed data analysis and manuscript preparation; JCS took care of data analysis and study design; NM, MO, and SM conducted the study and prepared the manuscript; GS conducted the study and recruited patients; MG provided patient recruitment technical and material support; CGG involved in study concept and design; MFV involved in study concept, design, and manuscript preparation.

REFERENCES

1 Locke GR 3rd, Talley NJ, Fett SL *et al.* Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997; **112**: 1448–56.
2 Dent J, El-Serag HB, Wallander MA *et al.* Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710–7.
3 Frye JW, Vaezi MF. Extraesophageal GERD. *Gastroenterol Clin North Am* 2008; **37**: 845–58. ix.
4 Vaezi MF, Hicks DM, Abelson TI *et al.* Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol* 2003; **1**: 333–44.
5 Vakil N, van Zanten SV, Kahrilas P *et al.* The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900–20. quiz 1943.
6 Fletcher KC, Goutte M, Slaughter JC *et al.* Significance and degree of reflux in patients with primary extraesophageal symptoms. *Laryngoscope* 2011; **121**: 2561–65.
7 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using

ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991; **101**(4 Pt 2 Suppl. 53): 1–78.
8 Francis DO, Rymer J, Slaughter JC *et al.* High economic burden of caring for patients with suspected extraesophageal reflux. *Am J Gastroenterol* 2013. (in press).
9 Ahmed T, Vaezi MF. The role of pH monitoring in extraesophageal gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am* 2005; **15**: 319–31.
10 Vaezi MF. CON: treatment with PPIs should not be preceded by pH monitoring in patients suspected of laryngeal reflux. *Am J Gastroenterol* 2006; **101**: 8–10.
11 Wiener GJ, Tsukashima R, Kelly C *et al.* Oropharyngeal pH monitoring for the detection of liquid and aerosolized supraesophageal gastric reflux. *J Voice* 2009; **23**: 498–504.
12 Sun G, Muddana S, Slaughter JC *et al.* A new pH catheter for laryngopharyngeal reflux: normal values. *Laryngoscope* 2009; **119**: 1639–43.
13 Ayazi S, Lipham JC, Hagen JA *et al.* A new technique for measurement of pharyngeal pH: normal values and discriminating pH threshold. *J Gastrointest Surg* 2009; **13**: 1422–9.
14 Chheda NN, Seybt M, Schade RR, Postma GN. Normal values for pharyngeal monitoring. *Ann Otol Rhinol Laryngol* 2009; **118**: 166–71.
15 Kawamura O, Aslam M, Rittmann T *et al.* Physical and pH properties of gastroesophagopharyngeal refluxate: a 24-hour simultaneous ambulatory impedance and pH monitoring study. *Am J Gastroenterol* 2004; **99**: 1000–10.
16 Williams RB, Ali GN, Wallace KL, Wilson JS, De Carle DJ, Cook IJ. Esophagopharyngeal acid regurgitation; dual pH monitoring criteria for its detection and insights into mechanisms. *Gastroenterology* 1999; **117**: 1051–61.
17 Vaezi MF, Schroeder PL, Richter JE. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. *Am J Gastroenterol* 1997; **92**: 825–9.
18 Shaker R, Bardan E, Gu C *et al.* Intrapharyngeal distribution of gastric acid refluxate. *Laryngoscope* 2003; **113**: 1182–91.
19 Wiener GJ, Koufman JA, Wu WC *et al.* Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-h ambulatory pH monitoring. *Am J Gastroenterol* 1989; **84**: 1503–8.
20 Adhami T, Goldblum JR, Richter JE *et al.* The role of gastric and duodenal agents in laryngeal injury: an experimental canine model. *Am J Gastroenterol* 2004; **99**: 2098–106.
21 Francis DO, Goutte M, Slaughter JC *et al.* Traditional reflux parameters and not impedance monitoring predict outcome after fundoplication in extraesophageal reflux. *Laryngoscope* 2011; **121**: 1902–9.
22 DeVault KR. Catheter-based pH monitoring: use in evaluation of gastroesophageal reflux disease symptoms (on and off therapy). *Gastrointest Endosc Clin N Am* 2005; **15**: 289–306.
23 Jamieson JR, Stein HJ, DeMeester TR *et al.* Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; **87**: 1102–11.

